

RECOMMENDATIONS

Recommendations for the use of bronchial thermoplasty in the management of severe asthma

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There are approximately 3 million asthma sufferers in South Africa, and the national death rate is ranked as one of the highest in the world. Approximately 5% have severe asthma (uncontrolled despite being adherent on maximal and optimised therapy). Such uncontrolled asthma is associated with high healthcare expenditure and may require treatment with anti-IgE and/or systemic corticosteroids, in addition to inhaler therapy and oral agents. These treatments may be costly, and those such as oral corticosteroids may have potential serious adverse events. There is therefore a need for more effective, affordable and safe therapies for asthma. A new modality of treatment, bronchial thermoplasty (BT), has recently been developed and approved for the treatment of severe asthma. BT involves delivering radio frequency-generated thermal energy to the airways, with the goal of reducing airway-specific smooth-muscle mass. Several clinical studies have confirmed that BT is effective and safe, that it improves control and quality of life in patients whose asthma remains severe despite optimal medical therapy, and that the beneficial effects are sustained for at least 5 years. We provide recommendations for the management of severe asthma, with an emphasis on the role of BT, and endorse the use of BT in patients with severe persistent asthma who remain uncontrolled despite optimal medical therapy as outlined in steps 4 and 5 of the British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN), UK National Institute of Clinical Excellence (NICE) and Global Initiative for Asthma (GINA) guidelines. We outline the context in which BT should be used, how it works, its associated potential adverse events and contraindications, and unanswered questions and controversies.

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1. The unmet need for interventions at treatment steps 4 and 5 of asthma guidelines

Over 300 million people suffer from asthma worldwide, and the prevalence of asthma is predicted to increase to over 400 million people globally by 2025.^[1] In South Africa (SA), approximately 8 - 10% of the population is asthmatic, and by country SA is ranked fourth highest in terms of asthma mortality.^[2] Of some 3 million SA asthma sufferers, approximately 5% have confirmed uncontrolled severe asthma despite being adherent to maximal and optimised therapy. Individuals with asthma that is difficult to control consume a disproportionate percentage (up to 80%) of asthma-specific healthcare expenditure owing to the high cost of hospitalisation, physician visits, and increased healthcare utilisation.^[3] Moreover, there is considerable morbidity, and an economic burden to patients and the state from days lost from school or work.

Currently proposed individual therapies at step 5 of the Global Initiative for Asthma (GINA) and British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines favour the use of oral corticosteroids (OCSs) and/or omalizumab. Maintenance treatment with oral or systemic corticosteroids is associated with serious adverse events such as osteoporosis, fractures and disability, an increased risk of serious or fatal infections including tuberculosis (TB), peptic ulceration, skin thinning, cataracts and diabetes, and their use should be avoided wherever possible. In SA, where the incidence of TB in many areas is >1 000/100 000 persons per year, the risk of TB is a particular concern.^[4] Omalizumab is an injectable monoclonal anti-IgE antibody recently approved for use in SA for patients with severe allergic asthma (confirmed by the presence of increased serum total IgE) uncontrolled on step 4 treatments. In those who respond (40 - 60% in the first few months), monthly injections may need to be continued indefinitely. The cost of omalizumab in SA is approximately ZAR175 428 per year (calculated in April 2015 for a person weighing 60 - 70 kg with an IgE level of

500 - 600 IU/L). Effective, affordable, and less toxic therapies are therefore urgently needed.^[5]

2. Bronchial thermoplasty: What is it and how does it work?

Bronchial thermoplasty (BT) is a device-based intervention that delivers thermal energy to the airways via a bronchoscopically guided catheter, with the goal of reducing airway smooth-muscle mass (Fig. 1). BT has been shown to increase the level of symptom control and improve quality of life in adults (>18 years) with severe asthma, with reductions in the frequency of exacerbations and asthma-related emergency room (ER) visits. BT was approved by the US Food and Drug Administration in 2010, and is included in several asthma treatment guidelines.^[6-8] It is viewed as complementary therapy rather than a replacement for pharmacotherapy, although drug replacement is achieved in some cases. BT is not curative, but aims to improve the quality of life of asthma sufferers and minimise the need for systemic corticosteroid therapy. It is performed as an outpatient hospital procedure over three treatment sessions by a trained pulmonologist under conscious sedation, after which the patient returns to the primary referring physician for long-term asthma management. The BT procedure itself has been outlined and reviewed in detail elsewhere^[9-11] and is summarised in Fig. 1.

The mechanism whereby BT achieves these clinical results is unclear. It may attenuate bronchoconstriction through altering the dynamics of airway smooth-muscle-induced bronchoconstriction. Indeed, airway narrowing in asthma in the context of smooth-muscle hypertrophy increases the airway resistance 20-fold when compared with resistance in normal airways.^[12] However, it seems unlikely that attenuation of bronchoconstriction alone is responsible for improvements, since improved lung function is not consistently seen. Animal studies have shown that airways treated at 65°C and 75°C, but not 55°C, show a reduction in airway responsiveness and smooth-muscle mass that persists for 3 years,^[13] and in human lungs this effect is seen as soon as 1 - 3 weeks after BT.^[14] BT therefore appears to influence lung remodelling and to have a disease-modifying effect. A recent study in ten patients with severe asthma has shown that 3 months after BT, a significant reduction in smooth muscle was observed not only in all the treated lung lobes but even in the untreated right middle lobe, which is not normally subjected to BT.^[15] Regression in smooth-muscle mass has therefore been demonstrated in the larger

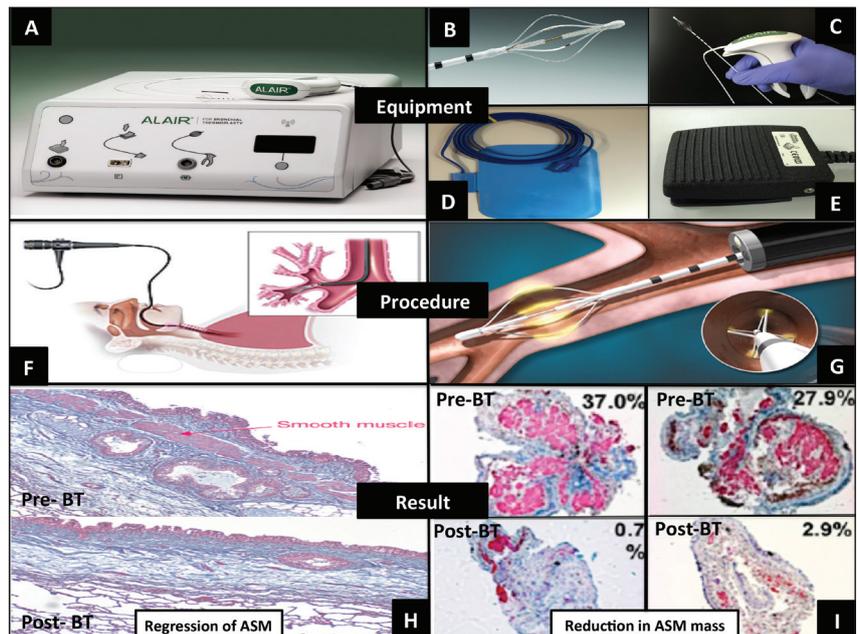


Fig. 1. Outline of the equipment, the BT procedure, and effects on airway smooth muscle. A: Alair radiofrequency controller; B: Alair BT catheter tip (basket electrode) with the 5 mm spacer markings guiding sequential activations; C: Handle grip controlling expansion of the catheter tip; D: Gel-type return electrode to complete the circuit; E: Foot pedal triggering delivery of the radiofrequency-mediated thermal energy; F: BT procedure performed using a flexible fiberoptic bronchoscope; G: Catheter in the bronchus delivering controlled radiofrequency thermal energy; H: Histological sections of dog bronchial wall before (top) and 12 weeks after BT (bottom), showing reduction in airway smooth muscle and preserved integrity of the epithelium, mucous glands and subepithelial tissue;^[13] I: Biopsies before and after BT in the lower lobes of two patients, showing reduction in airway smooth-muscle mass (the percentage of airway smooth-muscle surface area/total biopsy area) is shown numerically in the sub-figure. From www.btforasthma.com, reproduced with permission.

airways (>3 mm in diameter)^[13] and in the segmental and sub-segmental airways.^[15] The impact of BT on the more distal airways down to the level of the respiratory bronchioles, which also contain smooth muscle and are an important site of airway obstruction in asthma, remains unclear.^[16,17] The beneficial smooth-muscle-related effects may be due to several factors, including direct reduction in muscle mass, interference with contractile function, reduction in the secretion of inflammatory mediators from smooth muscle, reduction in muscle inflammation, a potential neural mechanism, disruption of a potential pacemaker effect, and possibly an indirect effect mediated by changes in the epithelium or other structures. However, there are hardly any data on the impact of BT on the immunopathology in human airways, or on the impact of other potential smooth-muscle-specific functions including immune modulation and angiogenesis. Interestingly, airway smooth-muscle regression associated with a reduction in exacerbations has also recently been demonstrated with the calcium channel blocker gallopamil.^[18]

BT is currently offered at 448 sites in 32 countries, and as of March 2015, more than

4 100 patients have been treated with BT (source: Boston Scientific). The use of BT for severe persistent asthma has now been endorsed by several guidelines, including the British Guideline on the Management of Asthma^[6] (BTS/SIGN), the UK National Institute of Clinical Excellence (NICE)^[7] and GINA^[8] guidelines, the European Respiratory Society/American Thoracic Society Guidelines on the Evaluation and Treatment of Severe Asthma,^[19] and the American College of Chest Physicians guideline.^[20]

This article seeks to clarify the recommendations of the South African Thoracic Society and its interventional pulmonology subgroup on how BT should be offered and used in the SA context. It is anticipated that this document will evolve and be updated as more evidence becomes available.

3. What do global and national guidelines say about BT?

Based on the available evidence (outlined in sections 5 and 6 below), BT has been endorsed by several international guidelines and professional societies. In the international 2014 joint European

Respiratory Society/American Thoracic Society (ERS/ATS) guideline on the definition, evaluation and treatment of severe asthma, and based on evidence that was evaluated to be strong but of low quality, the recommendation was for BT be performed in adults with severe asthma in the context of an independent institutional review board (research ethics committee)-approved systematic registry or clinical study.^[19] Contextually, this recommendation placed a higher value on avoiding adverse events, on increased use of resources and on a lack of understanding about which specific patients may benefit, and a lower value on improvement in symptoms and quality of life. The statement, prepared before the 5-year AIR2 (Asthma Intervention Study-2) data became available, reiterated the need for better understanding of the phenotypes of patients responding to BT and the effect that BT was having in patients with more severe obstructive asthma (forced expiratory volume in 1 second (FEV₁) <60% of predicted), or those in whom systemic maintenance OCSs are used.

The 2014 BTS/SIGN asthma guideline (British Guideline on the Management of Asthma) recommends that BT be considered for the treatment of adult patients who have poorly controlled asthma despite optimal therapy (grade A recommendation).^[6] It suggests that BT should be undertaken only in centres that have expertise in the assessment of 'difficult-to-control' asthma and in regularly performing fiberoptic bronchoscopic procedures, and reiterates the need for research that could better identify patients who could benefit from BT.

The 2014 UK NICE guideline endorses the use of BT, provided that patients understand the limitations in efficacy and longer-term safety (beyond 5 years) and the potential for adverse events.^[7] It further recommends that the details of all patients undergoing BT should be submitted to a 'difficult asthma registry', and emphasises that BT should be carried out by a respiratory team with special expertise in managing difficult and severe asthma.

The GINA revised 2014 report states that BT may be considered for some adult patients with severe asthma (evidence grade B).^[8] GINA states that BT is a potential step 5 treatment option in adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to a specialist asthma centre.

BT is endorsed by the Asthma and Allergy Foundation of America, which urges 'that health plans and insurance carriers fully cover the cost of BT for those whose severe asthma is not well managed by less invasive therapies, and whose physicians deem it appropriate'. BT has also been endorsed by INTERASMA, a global asthma association,^[21] which suggests that 'BT should not be considered as experimental but ... important option for patients ... and should be covered and paid by the social security system and/or private insurance to facilitate the accessibility for this special group of patients'. BT is now available in ~32 countries and is currently being funded or reimbursed by the national health system or medical insurance companies in the USA, Australia, the UK, Japan, Switzerland and Germany, among others. The American College of Chest Physicians has endorsed such reimbursement.^[20]

4. Recommendations and approach

4.1 Evaluate difficult-to-control asthmatics. Difficult-to-control asthmatics should be investigated to confirm the diagnosis of severe asthma (as per the ERS/ATS definition).^[19] We recommend that a high-resolution computed tomography (HRCT) scan of the lungs be performed to exclude alternative diagnoses or those precluding BT, including significant bronchiectasis, sarcoidosis, chronic obstructive pulmonary disease (COPD), endobronchial TB, bronchial stenosis, other endobronchial disease, tracheobronchomalacia, etc., which

may all masquerade as asthma. Other potential diagnoses such as vocal cord dysfunction, and comorbid conditions or other modifiable contributory or risk factors, such as gastro-oesophageal reflux disease, rhinosinusitis or use of concomitant medication or exposures that may subvert asthma control, should be considered. Further work-up may include other investigations to rule in alternative diagnoses or determine the underlying endotype, including total and specific IgE levels, exhaled nitric oxide (FeNO), blood and sputum eosinophilia, etc. At each visit, the patient's inhaler technique should be carefully checked, adherence to medication confirmed, and environmental modification implemented. These approaches cannot be overemphasised, as these factors frequently explain poor asthma control.

4.2. Optimise treatment. Patients should have a trial of at least 3 months' treatment with optimal and/or maximal doses of inhaled corticosteroids (ICSs) (ICS thresholds that define severe asthma are outlined in the ERS/ATS severe asthma guidelines^[19]), long-acting β_2 -agonists (LABAs) and/or long-acting muscarinic antagonists (LAMAs), and possibly other step 4 and 5 treatments (leukotriene receptor antagonists, and/or low-dose theophylline, and/or omalizumab (if appropriate)) in an attempt to optimise asthma control.^[6,7] In suitable patients with an appropriately raised serum IgE level and sensitivity to aeroallergens, a 4-month trial of omalizumab is advised.^[6,8] Immunosuppressive treatments such as methotrexate, cyclosporine, etc. are toxic but are included as treatments for severe asthma in some, but not all, guidelines;^[6,18] having limited efficacy, they are rarely used and should not be considered as routine treatment before considering BT. If used, they should be given for a minimum 3-month period, and stopped if there is no response to treatment.^[6]

While it is unnecessary to try all the abovementioned options, these steps are intended to ensure that any potential benefit from medical therapy is realised before recommending BT.

4.3 Confirm the diagnosis of severe asthma. If the patient remains uncontrolled despite appropriate work-up and optimisation of treatment as outlined in 4.1 and 4.2 above, a diagnosis of severe asthma can be established as per the ERS/ATS guideline,^[19] i.e. asthma that remains uncontrolled despite use of GINA step 4 or 5 therapeutic options (high-dose ICSs, LABAs, leukotriene modifiers, theophylline, omalizumab and/or OCSs).

4.4 Use of BT. We recommend that BT be considered and offered to patients who remain uncontrolled despite optimal therapy that includes maximal doses of ICSs and optimised GINA step 4 and 5 therapy (see 4.2 above).

4.5 Where should the procedure be performed, and by whom? BT should be offered to patients at a facility accredited by the Assembly on Interventional Pulmonology of the South African Thoracic Society and that has experience in dealing with difficult-to-control or severe asthma. The procedure should be performed by a pulmonologist experienced in performing bronchoscopy and BT. Patients should ideally form part of a national and/or international registry, or prospective study, so that long-term outcomes can be monitored and audited, and optimal patient selection is facilitated. Such a registry has been started in SA.

4.6 Recommendations for the procedure. Three sessions of BT approximately 3 - 4 weeks apart should be offered, preferably using local anaesthesia and conscious sedation where appropriate and if tolerated. General anaesthesia may be employed in appropriate patients. Periprocedural corticosteroids should be administered for a total of 5 days, beginning 3 days prior to the procedure. Prior to the procedure, spirometry should be performed to ensure that the post-bronchodilator predicted FEV₁ is within 90% of

the prior baseline. The procedure is relatively contraindicated in the presence of bronchiectasis because of the risk of infection. Other contraindications include the presence of an implantable pacemaker, defibrillator or other electronic device, sensitivity to any of the medications used during bronchoscopy, and any general contraindication to bronchoscopy, including those relevant to fitness, sedation and anaesthesia.

4.7 Post-procedural aspects. Patients should be closely monitored for exacerbations after the procedure, and those with a post-procedure $FEV_1 < 80\%$ of their pre-procedure baseline should be considered and carefully evaluated for possible hospitalisation should they continue to deteriorate (defined as persistently reduced lung function, suboptimal oxygen saturation, persistent tachycardia, etc.). A chest radiograph should be performed after the procedure if clinically indicated, e.g. in the case of suspected pneumothorax, segmental or lobar collapse, or suspected aspiration. Routine post-procedure chest radiography is unnecessary. Patients should be reassessed 6 - 12 weeks after their last BT procedure and regularly thereafter, and medication dosages, particularly of OCSs (if being used), should be reduced over time as appropriate, to the lowest dose that maintains asthma control. Patients may report an improvement in their symptoms as early as immediately after the first procedure. Increasing benefit after the second and third procedure is often reported.

4.8 Post-procedure follow-up. We suggest that all BT patients be enrolled in a national and international registry so that adverse events can be reported and audited. In the immediate post-procedure period (within 2 weeks), clinicians should be vigilant concerning complications such as asthma exacerbation, lung collapse and lung abscess. Data on long-term safety are accumulating.

5. What is the impact of BT on patient-related outcomes?

The clinical effectiveness of BT has been confirmed in two prospective cohort feasibility studies,^[14,22] three randomised controlled trials (RCTs),^[23-25] one of which was published in the *New England Journal of Medicine*, and three prospective cohort follow-up studies interrogating long-term outcomes and safety^[26-28] (the relevant studies are summarised in Table 1). The AIR trial enrolled 112 patients with moderate to severe asthma (FEV_1 60 - 85% of predicted).^[23] Patients with three or more lower respiratory tract infections (LRTIs) requiring antibiotics in the preceding year, or those with recent respiratory tract infections (RTIs), were excluded. The BT group showed a significant decrease in mild exacerbations (the primary outcome), significant improvement in asthma control (ACQ), significant improvement in quality of life (asthma quality-of-life questionnaire; AQLQ), and significantly increased symptom-free days.^[23] There was no impact on airway responsiveness or lung function.

The RISA (Research In Severe Asthma) open-label trial enrolled 34 patients with severe asthma ($FEV_1 > 50\%$ of predicted) and evaluated safety as the primary outcome.^[24] Patients with post-bronchodilator $FEV_1 < 50\%$ of predicted, > 3 LRTIs requiring antibiotics prior to BT, or a recent LRTI were excluded from this study. The study found that BT was well tolerated in severe asthma. The BT group showed an increase in pre-bronchodilator FEV_1 , improved asthma control (ACQ) and improved AQLQ scores, and significantly more subjects were weaned from OCSs (a 64% reduction in OCS use).^[24] The BT participants also had significant reduction in rescue medication use at 22 weeks.

The AIR2 study, designed specifically to minimise confounding and a placebo effect, enrolled 297 patients in a double-blinded sham-

controlled fashion, where all the enrolled patients had a bronchoscopy and catheter insertion, but radiofrequency-generated thermal energy was not delivered to the airways in the control group (sham).^[25] This study enrolled patients with severe asthma ($FEV_1 > 60\%$ of predicted and using $> 1\ 000\ \mu\text{g}$ beclomethasone per day with or without OCSs and omalizumab). Patients with ≥ 3 prior hospitalisations, ≥ 3 LRTIs in the previous year, ≥ 4 pulses of OCSs in the previous year, previous life-threatening asthma, or a need for ≥ 10 mg of OCSs per day were excluded from the study. The primary outcome was the change in the AQLQ. The study found significantly greater patient-level improvement in AQLQ in the BT group, and secondary outcomes (severe exacerbations and ER visits) were significantly reduced in the BT group. Pre-bronchodilator FEV_1 did not improve significantly, however, and rescue medication use did not decrease significantly in the BT group. In addition to the reduction in severe exacerbations during the 12-month follow-up period, asthma-related days lost from work, school or other activities were also significantly reduced in the BT group. Notably, there was a strong placebo effect in the sham-treated subjects.

A Cochrane-based systematic review and meta-analysis incorporating all three RCTs concluded that BT in patients with moderate to severe asthma provided modest clinical benefit, improved quality of life, and lowered rates of asthma exacerbation.^[29] However, the procedure increased the risk of adverse events during treatment but had a reasonable safety profile after treatment. The authors rated the overall quality of evidence regarding BT as 'moderate'. They suggested that 'future research would provide better understanding of the mechanisms of action of BT, as well as its effect in different asthma phenotypes, or in patients with worsening lung function'. There are currently no data on the impact of BT on mortality in severe asthma, but it is noteworthy that the percentage of the bronchial wall occupied by smooth muscle is increased in fatal asthma (12% in segmental bronchi v. 5% in normal subjects).^[30]

6. What is the response rate and who is most likely to respond?

In the AIR2 study, 78.9% of BT patients recorded at least a 0.5 change in AQLQ score, and there was a ~53% reduction in ED visits for BT patients, a ~35% reduction in severe exacerbations experienced, and a ~50% reduction in respiratory-related hospitalisations.^[27] In several respects, the magnitude of changes are not dissimilar to that seen with omalizumab (e.g. a ~25% reduction in exacerbations, and a 70% reduction in ED visits).^[31-33]

6.1 Who is most likely to respond? In a recent study, Sheshardi *et al.*^[9] showed that a good response to BT was associated with more gas trapping on HRCT, reduction in specific quantities of ICSs or OCSs, and an incremental improvement in the AQLQ score of > 0.5 . The pathogenesis of bronchial asthma is complex and is broadly characterised by an interrelating combination of smooth-muscle dysfunction, airway remodelling, and T-helper (Th)2- and non-Th2-related inflammation.^[34] Several subgroups of bronchial asthma have now been described, including those with high symptom counts but minimal eosinophilic inflammation, and those that are inflammation dominant but have fewer daily symptoms.^[35] Phenotypes may also be categorised based on biomarker profiles, and some biomarkers (e.g. blood eosinophils, serum periostin, IgE levels, FeNO, etc.) predict response to therapy with biological agents that target specific inflammatory pathways.^[34,36-38] It remains unclear what clinical phenotype (e.g. obese v. non obese; those with airway hyper-responsiveness (AHR) v. those without), endotype or molecular phenotype (e.g. atopic v. non-atopic or Th2 v. non-Th2), or genotype is most likely to respond to BT.^[38] The value of specific biomarkers

Table 1. Summary of key clinical studies evaluating the safety, efficacy and long-term outcomes of BT

Study details	Key inclusion criteria	Key exclusion criteria	Efficacy measures	Adverse events	Comments
Miller <i>et al.</i> , ^[14] 2005 Number enrolled: 16 Design: Feasibility study	Patients with suspected or proven lung cancer scheduled for lung resection	N/A	Safety, airway smooth-muscle mass reduction in the resected lung segments	No serious adverse events	Decrease in airway smooth muscle documented
Cox <i>et al.</i> , ^[22] 2006 Number enrolled: 16 Design: Feasibility study	Adults with mild to moderate asthma	Recent RTI, frequent use of rescue medication	Safety, methacholine PC20 at 2 years post BT	No serious adverse events, no hospitalisations	Mean PC20 increased post-BT, increase in symptom-free days, morning and evening peak flows remained stable
AIR trial ^[23] (Cox <i>et al.</i>), 2007 Number enrolled: 112 Design: RCT	Adults ≤65 years with moderate to severe asthma (FEV ₁ 60 - 85% predicted)	Recent RTI and ≥3 or more LRTIs requiring antibiotics in the preceding year	Primary: rate of mild asthma exacerbation Secondary: ACQ/AQLQ	Asthma worsening post BT requiring hospitalisation (7.6% BT v. 4.08% control group), but rates of adverse events between 6 weeks and 12 months were equal in the two groups	Decrease in mild exacerbations, improvements in ACQ/AQLQ scores, and increase in symptom-free days
RISA trial ^[24] (Pavord <i>et al.</i>), 2007 Number enrolled: 34 Design: RCT	Adults ≤65 years on high-dose ICS/LABA with AHR and uncontrolled symptoms (FEV ₁ <50% of predicted)	Post-BD FEV ₁ <50% of predicted, >3 LRTIs requiring antibiotics prior to BT, and those who had a recent LRTI	Primary: safety Secondary: ACQ/AQLQ, OCS and ICS dose reduction, and FEV ₁	Hospitalisation in 4/17 patients (23%) in the BT group v. none in the control group, mostly within 3 days of BT procedure, but similar rates of hospitalisation in post-treatment phase compared with control group	Overall BT well tolerated in severe asthma, increase in pre-BD FEV ₁ , increase in ACQ/AQLQ scores, and increased proportion of OCS weaning post BT
AIR2 trial ^[25] (Castro <i>et al.</i>), 2008 Number enrolled: 297 Design: RCT – double blind sham controlled	Adults ≤65 years on high-dose ICS/LABAs (FEV ₁ >60% of predicted)	Previous life-threatening asthma, ≥3 prior hospitalisations or LRTIs in the previous year, ≥4 or more pulses of OCSs in the previous year, need for ≥10 mg of OCSs per day	Primary: change in AQLQ Secondary: severe exacerbations, healthcare utilisation	Increased rate of hospital admissions (8.4% in the BT group v. 2% in the control group)	Greater increase in AQLQ in BT group, decrease in severe exacerbation and asthma-related ER visits in BT group
AIR 5-year follow-up ^[26] (Thompson <i>et al.</i>), 2011 Number enrolled: 45 Design: Prospective cohort	As above	As above at baseline	Adverse events, hospitalisation, FEV ₁ and FVC	No long-term adverse events	Absence of reported clinical complications, no increase in asthma-related healthcare utilisation, stable FEV ₁ and FVC over 5 years
RISA 5-year follow-up ^[27] (Pavord <i>et al.</i>), 2013 Number enrolled: 14 Design: Prospective cohort	As above	As above at baseline	Safety, severe exacerbations, lung function	No long-term adverse events	Decrease in asthma-related ER visits, hospitalisations and FEV ₁ maintained post BT
AIR2 5-year follow-up ^[28] (Wechsler <i>et al.</i>), 2013 Number enrolled: 162 Design: Prospective cohort	As above	As above at baseline	Safety, asthma control, severe exacerbation, asthma-related ER visits	No long-term adverse events	Decrease in severe exacerbation, asthma-related ER visits and hospitalisations post-BT maintained over the follow-up period

N/A = not applicable; PC20 = provocative concentration (concentration of methacholine at which the FEV₁ falls by ≥20%); FVC = forced vital capacity.

to predict response to BT therefore requires clarification. As already outlined, severe asthmatics with previous life-threatening asthma, OCS requirements of >10 mg/d and >3 - 4 exacerbations or hospitalisations in the preceding year were excluded from the clinical trials. Such patients are frequently seen in severe asthma clinics in day-to-day clinical practice, and studies on the effect of BT in this specific subgroup of patients are urgently required. Prospective studies will be required to delineate exactly which phenotype of patient is most suitable for and responsive to BT.

7. What adverse events are associated with BT?

In the AIR study, four of 66 subjects in the BT group (6%) were hospitalised (six hospitalisations).^[23] In the RISA trial, four of the 17 BT-treated patients had seven hospitalisations, of which two were secondary to the development of segmental lobar collapse, and one patient required bronchoscopic aspiration of mucus.^[24] In the AIR2 study, in which 850 bronchoscopies were performed (558 BT and 292 sham procedures), there were no device-related deaths or major adverse events such as pneumothorax, exacerbations requiring mechanical ventilation, airway stenosis or focal airway narrowing. However, during the within-BT treatment period, hospitalisation occurred more frequently in the BT group (8.4%) than in the sham bronchoscopy group (2%).^[25] It is clear from these studies that BT can be associated with complications requiring immediate post-procedure hospitalisation due to an asthma exacerbation. Periprocedural corticosteroids (administered 3 days before, on the day, and 1 day after) are given to minimise this risk. The risk of hospitalisation must be balanced against the long-term clinical improvements achieved, including reductions in exacerbations, absenteeism and corticosteroid use.

The long-term safety of BT (up to 5 years) has been demonstrated in three studies.^[26-28] There is no consistent evidence that BT is causally associated with bronchial stenosis or bronchiectasis. In the AIR2 follow-up study, only three of 93 patients developed new ($n=1$) or worsening bronchiectasis ($n=2$) as shown on HRCT; it remains unclear whether this was a complication of asthma or related to BT. Minor bleeding in the airways may sometimes be seen during the procedure, but haemoptysis is rare (one patient in the AIR2 study developed major haemoptysis requiring embolisation

Table 2. Unanswered questions and outstanding controversies regarding BT

1	What is the mechanism whereby BT reduces smooth-muscle mass in humans and animals, and what is its effect on different cellular and structural components of the human airway?
2	What specific phenotypes of severe asthma that remain symptomatic despite optimal treatment will best respond to BT?
3	Do patients with more severe persistent asthma, who were excluded from the clinical trials, benefit to the same extent, or more, from BT?
4	Does BT have increasing benefit in those who have partially responded or in whom the benefit later lapses?
5	How far beyond 5 years does the BT effect last?
6	Can the same effect be obtained in fewer BT sessions?
7	Is there any incremental benefit from more than three BT sessions, and what parameters portend room for further response?
8	In patients with atopic severe persistent asthma and who are suitable for omalizumab (or in future other biologicals), should BT be offered in the first instance taking into account their comparative efficacy, safety and cost?
9	Are there longer-term (beyond 5 years) safety issues in patients who undergo BT?
10	Should BT should be recommended in an earlier treatment step to attempt to reduce costs of multiple drug treatments and the potential morbidity of prolonged uncontrolled asthma, or must it be undertaken as a last resort at step 5 when all else has failed?
11	What is the relationship between asthma severity, and other biological factors, and the probability of post-procedure complications?
12	Will patients with emphysema or the asthma-COPD overlap syndrome benefit from BT, and what parameters should be used to guide the decision to employ it?

about 1 month after bronchoscopy).^[25] A recent case report describes a lung abscess that occurred during the first week after a single BT treatment session,^[39] and another reports recurrent atelectasis caused by fibrin plugs.^[40] These published cases indicate the need to remain vigilant during the post-procedure period.

8. Is the effect of BT sustained, and is it cost-effective?

Two prospective cohort studies have shown that the beneficial effects of BT are sustained.^[27,28] A follow-up of the RISA cohort demonstrated that the reductions in hospitalisations (70% reduction) and ER visits (~66% reduction) were sustained for 5 years.^[27] There was no long-term change in the predicted FEV₁. A follow-up of the AIR2 cohort showed that the reduction in severe exacerbations (38% reduction, i.e. 52% in the 12 months preceding BT and ~30% for each year of the follow-up period) and ER visits (88% reduction) post BT were also sustained for 5 years.^[28] Although no comparison with the control groups was made during this follow-up study, the results at least confirm sustained benefit across several endpoints.^[41]

The estimated comparative 2015 cost of BT, including bronchoscopy and physician visits at the time of writing, was estimated to

be ~ZAR120 000, being a one-time cost. A cost-effectiveness study in the USA showed that in poorly controlled severe persistent asthma, with a 5-year view in the base-case scenario, the cost-effectiveness of BT was USD5 495 per quality-adjusted life-year, which was below the 'willingness to pay' threshold of USD50 000 in the USA.^[42] Further cost-effectiveness studies are required in different contexts.

9. Unanswered questions and controversies

The AIR2 study^[41] has been criticised for several reasons. Firstly, as already mentioned, it excluded patients with more severe asthma who would possibly have benefited the most from BT; only 3.7% of patients undergoing BT in AIR2 were on OCSs, a group that may be considered to have more severe asthma, although otherwise the patients enrolled met the minimal criteria for the definition of severe asthma.^[25] Secondly, although there was potentially significant improvement in the predetermined AQLQ-specific primary outcome (mean difference of 0.19 between the groups), this fell below the threshold for a clinically meaningful difference (change in AQLQ score >0.5); however, when analysed differently, i.e. at an individual level (percentage of subjects with an AQLQ

change of >0.5), AQLQ was statistically significantly better in the BT-treated than in the sham bronchoscopy group (78.9% v. 64.3%). The latter approach is justified when interpreting AQLQ scores, which reflect within-group differences better than between-group differences.^[11] Thirdly, the placebo effect is well recognised in asthma trials, and the AQLQ improvement in the sham group was probably due to more meticulous and protocol-driven asthma care during the trial, as well as standardisation of care before recruitment. Given this consideration, the AIR2 study should ideally have incorporated a longer run-in period, and in retrospect, chosen asthma exacerbation or ER visits as an *a priori* primary outcome. Indeed, there was a significant reduction in exacerbations and ER visits, but this was a secondary outcome rather than a prespecified primary outcome.^[25] Nevertheless, the reduction in severe exacerbations was significant, and this is an important determinant of patient-related quality of life and utilisation of healthcare costs. Fourthly, it has been suggested that there were outliers in the control group that could have driven a meaningful part of the statistical difference between the groups. However, it was clarified that removal of the outlier would still substantially reduce ER visits from 84% to 70%. These points have been openly debated and are outlined in detail in several editorials and letters to the editor.^[41,43] Other unanswered questions are outlined in Table 2. These include questions related to the mechanism of action of BT and the identification of patients most likely to benefit from it.

Conclusions

BT is indicated as a treatment for severe asthma that remains uncontrolled despite an optimal trial of step 4 and 5 GINA therapeutic options.^[8] BT has been shown to significantly lower the rates of asthma exacerbation and ER visits, and has shown modest benefits in improvement of quality of life scores. The procedure has been confirmed to be safe with no significant long-term adverse effects up to 5 years after the initial intervention. Complications of BT include exacerbations and hospitalisation due to transient worsening of asthma symptoms in a small proportion of patients. As this treatment is directed towards treating severe asthma, further studies are needed to establish both its short-term and longer-term safety (beyond 5 years) in patients with more severe disease, and those features that identify patients most likely to benefit from BT.

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